February 8th

Dear Mike:

Many thanks for your recent letter; it was comforting to receive it and to know that I will be welcome to use some bench space in your laboratory. I was also comforted by your optimistic words about GMAG's attitude towards cloning of viral DNA. On the same day, I received a similarly buoyant note from Ed Southern, with whom I have been corresponding for several weeks about the possibility of doing some collaborative experiments to clone the integration sites for avian sarcoma virus DNA in transformed mammalian cells. (This work, if permitted, will be carried out primarily by a post-doctoral fellow here---Steve Hughes---who will travel to Edinburgh for the sensitive part of it.) Although your optimism extends to src, we are being rather cautious and hoping for the moment to obtain permission to clone the ends of the provirus (with very little viral information, all outside src) plus attached cellular sequences. I'll keep you informed about the progress of our application.

I will be curious to hear whether the possible easing of restrictions would now incline you to greater interest in cloning some RNA tumor virus genes. As I mentioned previously, I would think that cloning endogenous mouse mammary tumor virus DNA in polyoma would be an approvable goal and presumably consistent with your

ambitions to catalogue the murine genome. We are getting very close to a map of the 3-5 copies of endogenous MMTV DNA per haploid genome; the best estimates are that the copies represent complete or almost complete proviruses which have considerable similarity and a surprising degree of homologous flanking material. (E.g., Hpa I yields only two fragments containing virus-specific sequences and these have a combined molecular weight of about 9×10^6; Hpa I thus appears to cut once (ca. 6×10^6 Mr) in each endogenous provirus/and then within homologous adjacent regions. Eco RI yields about 8 fragments of high molecular weight; it too cuts once within the proviruses, but the cuts in cellular DNA reveal differences in the adjacent host sequences. These differences are not surprising, since we have recently found that the proviruses are on multiple (> 1) chomosomes.) Of course, we are also interested in cloning integration sites for newly-acquired proviruses of MMTV, both in mouse and heterologous cells, with particular interest in the specificity of integration and the regulatory elements which govern steroidal control of transcription. I look forward to discussing some of these possibilities with you in July.

When you return from the States (you are probably already back), perhaps you would have a few moments to speculate on the current status of cloning in polyoma vectors and on how I might be useful to you in a way that would allow me to learn to use the system.

With best regards,

Harold